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Fabrication and in-vitro characterization of mucoadhesive tablet using a natural biocompatible polymer containing metformin HCl

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ABSTRACT

Background: Drug delivery mucoadhesion has been a subject of study for decades, initially focusing on understanding processes and investigating polymers. Mucoadhesive tablets are oral dosage forms that adhere to mucosal surfaces, promoting prolonged contact and localized drug delivery. **Aim and Objective:** A mucoadhesive tablet formulation of metformin could enhance drug delivery and improve therapeutic outcomes for patients with type 2 diabetes. **Material and Method:** The wet granulation process is used to develop mucoadhesive tablets by developing granules with the ideal characteristics for compression and tablet production. The process involves the use of natural mucoadhesive polymers like pectin and xanthan gum, along with the active component of metformin. Various testing techniques, such as weight variation, friability, hardness, DSC, TGA, XRD, in vitro dissolution, and release kinetics, are used to evaluate mucoadhesive tablets. **Result and Discussion:** Most formulations exhibited optimal test results within official limits in terms of friability, weight variation, and hardness. Thermal analysis indicated a transition within the temperature range, showed an exothermic peak in DSC analysis, and demonstrated temperature stability in thermogravimetric analysis. In vitro dissolution studies revealed exceptional drug release, reaching approximately 101% over 12 hours. The release kinetics modeling, performed through regression analysis, indicated sustained release. The n-exponent of the Korsmeyer and Peppas models suggested Fickian drug release. **Conclusion:** The successfully synthesized mucoadhesive tablets, formulated with natural and biocompatible mucoadhesive polymers, exhibit optimal drug release properties. They are utilized for

prolonged drug release for up to 12 hours, aiding in diabetic management through metformin.

Keywords: Natural polymers, mucoadhesion, Metformin, diabetes type-II, sustained release.

1. INTRODUCTION

Mucoadhesive drug delivery methods extend the duration of the dosage form's residence at the absorption site by adhering to the mucus layer and interacting with mucin molecules. Drugs designed for local action or optimal absorption in the gastrointestinal tract (GIT) benefit from an extended duration within the GIT. Hence, mucoadhesive dosage forms offer advantages in elevating drug plasma concentrations and therapeutic efficacy (Boddupalli et al., 2010). The attachment of artificial or biological macromolecules to biological tissues—mainly the mucus layer—is known as mucoadhesion. It happens when a polymer and membrane interact closely, either via wetting or swelling (Boddupalli et al., 2010).

Mucoadhesive polymers consist of water-soluble and water-insoluble components, forming expandable networks interconnected by cross-linking agents. These polymers exhibit optimal polarity (Menczel et al., 2008). Mucoadhesive polymers are crucial in drug delivery systems due to their non-toxic, non-absorbable properties and affinity for mucin and epithelial cells (Menczel et al., 2008). Xanthan gum and hydrophilic polymers such as HPMC form a viscous gel layer, which controls drug release. Combining these polymers enhances mucoadhesive drug delivery, enabling sustained release over more extended periods, particularly for chronic conditions, thereby enhancing therapeutic effectiveness (Wu et al., 2008).

Pectin, a naturally occurring carbohydrate polymer, is renowned for its gelling and adhesive properties and is a crucial structural element found in citrus byproducts (Wu et al., 2008). T2DM, a global metabolic disorder, presents a significant health threat worldwide due to its widespread prevalence in the 21st century (Unnikrishnan et al., 2017). Metformin stands out as the most prescribed antidiabetic medication for managing type 2 diabetes, owing to its efficacy, cost-effectiveness, and safety. In contrast to the discontinuation of phenformin and buformin due to adverse effects, metformin has remained in use. It is a three-time-a-day drug that was developed into sustained-release tablets, aiming to reduce non-adherence among diabetic patients and thereby enhance treatment effectiveness (Giannarelli et al., 2003).

With some cases showing promising results, metformin has been proven effective in treating various diseases like aging, cancer, polycystic ovarian syndrome, heart failure, and obesity (Shurrah and Arafa, 2020). This research aims to develop and evaluate a medication that increases the duration of residence in the gastrointestinal system to improve drug bioavailability. By eliminating the necessity for repeated doses, the dosage form aims to improve patient compliance. The dosage form is expected to improve therapeutic efficacy by enhancing interaction with the underlying absorption surface and prolonging the residence duration at the absorption site.

2. MATERIALS AND METHODS

Ingredients

This formulation uses metformin HCl, xanthan gum, pectin, magnesium stearate, talc, and microcrystalline cellulose (MCC). Sigma-Aldrich in Germany provided all the components. Furthermore, isopropyl alcohol and distilled water were also used. All materials were of analytical grade and used exactly as provided.

Equipment's

For the production process, tools, including polyethylene bags, a drier, a mortar and pestle, Wattman filter paper, and sieves with different sieve numbers, are required. The instrumentation for this process comprises a ZP-17 tableting machine, a weighing balance, a stirrer, a dissolution apparatus, a UV spectrophotometer, an FTIR spectrometer, and a disintegration apparatus.

Method of Preparation

The study spanned eight months, from February 10, 2023, to December 15, 2023. Ethical approval for the study was obtained from Lahore Pharmacy College, Lahore, Pakistan, with reference number (ref: RMEC/ZA/05032), ensuring compliance with ethical standards and guidelines. Using isopropyl alcohol, wet granulation is a possible technique to develop mucoadhesive metformin tablets. The

powders (F1–F9) were either combined and granulated using isopropyl alcohol or mixed with an adhesive to form a wet mass. To produce granules, the moist material was dried and then sized. After the damp bulk was run through sieve 16 with a mesh size of 1000 µm, the granules were dried at 50°C for two hours.

After forming the wet mass, further treatment was carried out to obtain dry granules with a specific particle size. The dried granules were passed through filter no. 25 (650 µm) and lubricated with a combination of talc and magnesium stearate in particular proportions. To compress the lubricated granules, a ZP-17 tableting machine was then used. Wet granulation is a technique that produces porous tablets with improved cohesive properties, enabling drug release in the stomach and upper gastrointestinal tract. It prevents powder segregation, enhances tablet compression, and improves material flow. Table 1 shows the composition of several formulations.

Table 1 Formulation Table

Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)
Metformin HCL	250	250	250	250	250	250	250	250	250
Xanthan Gum	300	350	---	---	100	200	150	175	170
Pectin	---	---	300	350	200	100	150	150	170
Mg stearate	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5
Talc	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
MCC	40	-	40	-	40	40	40	15	-
Total weight(mg)	600	600	600	600	600	600	600	600	600

Characterization

Pre-Formulation studies

Melting Point

The medication powder is measured precisely, then applied to the hot plate surface, cleaned, and the temperature is progressively raised. In contrast, the powder's melting point is monitored and noted on a thermometer (Jannot et al., 2010).

Precompression studies

The analysis of flow properties includes several techniques, such as:

Carr’s Index/Compressibility Index

After weighing the ingredients, move them into a measuring cylinder. Determine the bulk volume (VB) without tapping, then tap until it reaches a constant volume, record the tapped volume (Vt), and use Carr's equation to calculate the compressibility index (Mustafa et al., 2023a). The following formula may be used to determine Carr's index.

Carr’s index = (Tapped density –Bulk density /Tapped density) *100

Hausner’s Ratio

To administer the medication, take 1 gram and place it in a 10 ml measuring cylinder. Record the initial volume of the drug in the cylinder. Using a USP bulk density apparatus, tap the measuring cylinder 50 times (Mustafa et al., 2023a). Use the following formulas to determine the bulk density and tap density:

Bulk density = $\frac{\text{Weight of the microspheres}}{\text{Initial volume}}$

Tapped density = $\frac{\text{Weight of the microspheres}}{\text{Final volume after tapping}}$

Calculate the Hausner's ratio using the following formula:

$$\text{Hausner's ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

Angle of Repose

The fixed funnel was utilized at a height of 2.5cm (H) above a level surface, and paper was placed beneath. After pouring the powder through the inverted funnel, the diameter was found (Mustafa et al., 2023a). The angle of repose is determined through the following formula.

$$\text{Angle of repose} = \tan^{-1}\left(\frac{2h}{d}\right)$$

Solubility Analysis

pH Solubility Profile

Weighing was done using four China plates (W1). The drug was dissolved in a pH 5.8 buffer until saturation, then filtered through Whatman filter paper and collected in a china dish. The filtrate was heated until crystallization occurred, after which it was weighed as W2 using tongs on a scale. This procedure was repeated for pH buffers 6.8, 7.4, and 8, followed by further computations (Sarkar et al., 2017).

Partition Coefficient

Incorporate the drug into the immiscible solvents. Agitate the separating funnel for at least 30 minutes. Without stirring, allow the mixture to settle for twenty minutes. Examine the separation of the two phases. Extract each solute individually. Use the below formula to determine the partition coefficient:

$$\lambda_{\text{max of metformin}} = 232\text{nm}$$

Measure the maximum wavelength (λ_{max}) of metformin using a spectrophotometer (Sarkar et al., 2017).

Preparation of Calibration Curve

To prepare a standard solution of metformin, weigh 50mg of metformin and dissolve it in 50 ml of distilled water. Next, pure water is used to dilute 2.5 milliliters of this solution to 25 milliliters. Ten milligrams of the resultant solution will be present per milliliter. Fill a cuvette with pure water and set the spectrophotometer to auto-zero to guarantee reliable absorbance measurements. To determine metformin concentration in an unknown sample, create a calibration curve, which is a concentration versus absorbance graph. This step guarantees precise and reliable results in the analysis of metformin formulations (Sarkar et al., 2017).

Post-Formulation studies

Weight Variation

For a weight variation test, twenty tablets from each formulation were selected and individually weighed on a weighing balance. The combined weight of 20 tablets and the weight of each tablet on average was calculated. Afterward, the weight of each tablet was compared to the average weight to determine any variations (Dhar and Pokharkar, 2010).

Friability Testing

Friability is the weight reduction and potential fracture of a tablet during transportation. By using the Roche Friabilator device, the friability of five tablets of each formulation was tested by weighing. The apparatus was cleaned, and the test was set to 25 rpm for four minutes. After four minutes, the tablets were removed and re-weighed (Mustafa et al., 2023b). To determine the friability, the following formula was used

$$\text{Friability} = \frac{\text{Initial weight (W1)} - \text{final weight (W2)}}{\text{Initial weight (W1)}} \times 100$$

Hardness Testing

The hardness of a tablet is measured in kg/m² using a digital galvanic hardness tester. The tablet is placed between the jaws, and pressure is applied until it breaks. Five tablets from each formulation are selected, and the average weight is recorded (Dhar and Pokharkar, 2010).

Tablet Thickness and Diameter

Choosing five tablets from each formulation, snapping the jaws of the Vernier caliper shut, and recording the primary scale reading are the steps of the test. The Vernier scale reading (VSR) is determined by aligning a tablet between the middle jaws and dividing the Vernier scale to align with the main scale. Therefore,

$$\text{VSR} = \text{Vernier scale coincidence} * \text{least count}$$

After determining the VSR for each tablet, the primary scale reading is combined with the Vernier scale reading, and the average value is then calculated (Dhar and Pokharkar, 2010).

Disintegration Test

The disintegration test involved placing six tablets in a 1.2 HCl buffer, similar to a human gastric fluid, and moving the basket at 29-32 cycles per minute. The temperature remained constant at 37°C. The time it took for the tablets to dissolve was recorded, and any remaining tablets were examined to ensure no fragments remained (Mustafa et al., 2023a).

Differential Scanning Calorimetry (DSC) Analysis

DSC experiments were performed on the chosen tablet formulation. Samples weighing 3–4 mg were heated at a rate of 10°C/min in an aluminum pan until they reached a maximum temperature of 300°C. The device was calibrated using indium, and the carrier gas used was dry nitrogen at a flow rate of 25 milliliters per minute. For confirmation, the test was conducted again (Ahmed et al., 2023).

Thermal Gravimetric Analysis (TGA) Analysis

Thermogravimetric analysis (TGA) was performed on the mucoadhesive formulation using a TGA 2950 instrument. At a rate of 5 °C per minute, the sample, weighing 3 mg, was heated from room temperature to 500 °C (Ahmed et al., 2023).

X-ray Diffraction (XRD) Analysis

The crystallinity of metformin and polymers was evaluated using an X-ray diffractometer. Polymers were scanned from 5° to 80° diffraction angle (2θ) under the specified measurement conditions: Cu K radiation source ($\lambda = 1.5418\text{\AA}$), 40 kV voltage, 30 mA current, 5°/min scan rate, 1.25° division slit, and 0.3 mm reception slit (Bahulkar et al., 2015).

In vitro Dissolution

The dissolution test involves filling a vessel with a simulated gastric fluid and placing a tablet inside. The paddle rotates at 37°C and 50 rpm. Samples are taken at different intervals, diluted with a dilution factor of 10, and then transferred to a UV-visible spectrophotometer for analysis. The mucoadhesive tablet's drug release profile is established over time. Using pure water to zero the spectrophotometer, each dilution is conducted one at a time. By calculating the drug's percentage release at each time point, a percentage release curve is developed, providing an overview of its release over time (United States Pharmacopeia, 2017).

Release Kinetics

Using the DD-Solver add-in program, various kinetic models, including zero-order, first-order, Korsmeyer, and Peppas, are used to calculate the drug's release kinetics from the dosage form. On the behavior and pattern of drug release, evaluation is done (Wójcik-Pastuszka et al., 2019).

3. RESULTS

Pre-Formulation studies

Melting point

The Melting Point of metformin observed was 223°C.

Pre-Compression Studies

The formulas from F1 to F3 showed poor flow characteristics, according to the data. The pre-compression characteristics of formulations F4–F5 were satisfactory but not exceptional. Table 2 displays these outcomes. Results for formulations F6 to F9 fell within the acceptable range. The readings for bulk density, Hausner's ratio, tapped density, Carr's index, and angle of repose were all good to exceptional. Among the three tested formulations (F7–F9), F9 performed the best and exhibited the most fitting results within the official limits.

Table 2 Pre-Compression Studies

Formulations	F1	F2	F3	F4	F5	F6	F7	F8	F9
Angle of Repose (°)	20.56±0.04	22.19±0.067	35.89±0.051	56.21±0.079	46.8±8.0	56.8±8.0	32.1±5.6	28.9±3.2	28.8±1.9
Flow Rate (g/s)	30.0±0.8	35.0±0.6	3.0±0.8	38.0±0.5	32.0±0.8	33.0±3.3	3.8±1.3	35.1±7.1	4.3±0.3
Carr Index (%)	16.84±0.03	18.49±0.094	16.63±0.065	17.24±0.074	16.4	16.7	21.4	17.5	13.2
Hausner Ratio	1.20	1.18	1.17	1.20	1.2	1.2	1.3	1.2	1.15

Partition coefficient

Metformin is hydrophilic, as a significant portion of the drug is present in the solution's water phase.

pH solubility profile

As shown in Table 3, metformin showed exceptional solubility in dissolving agents, especially in phosphate buffer (pH 7.4).

Table 3 pH solubility profile

Sr No	pH buffer solution	A gram of drug soluble in mL of buffer	Degree of solubility
1	1.2	1 in 13.5 parts	Freely soluble
2	5.4-5.8	1 in 12.9 parts	Freely soluble
3	6.8	1 in 30.5 parts	Soluble
4	7.4	1 in 12.5 parts	Very soluble

Calibration Curve Data

Table 4 provides concentration vs. absorbance data for the metformin tablet test solution, and Figure 1 shows the corresponding graph.

Table 4 Absorbance and concentration data

Sr.no.	Concentration (µg/ml)	Absorbance
1	14	1.51
2	16	1.63
3	20	1.808
4	22	1.917
5	26	2.059

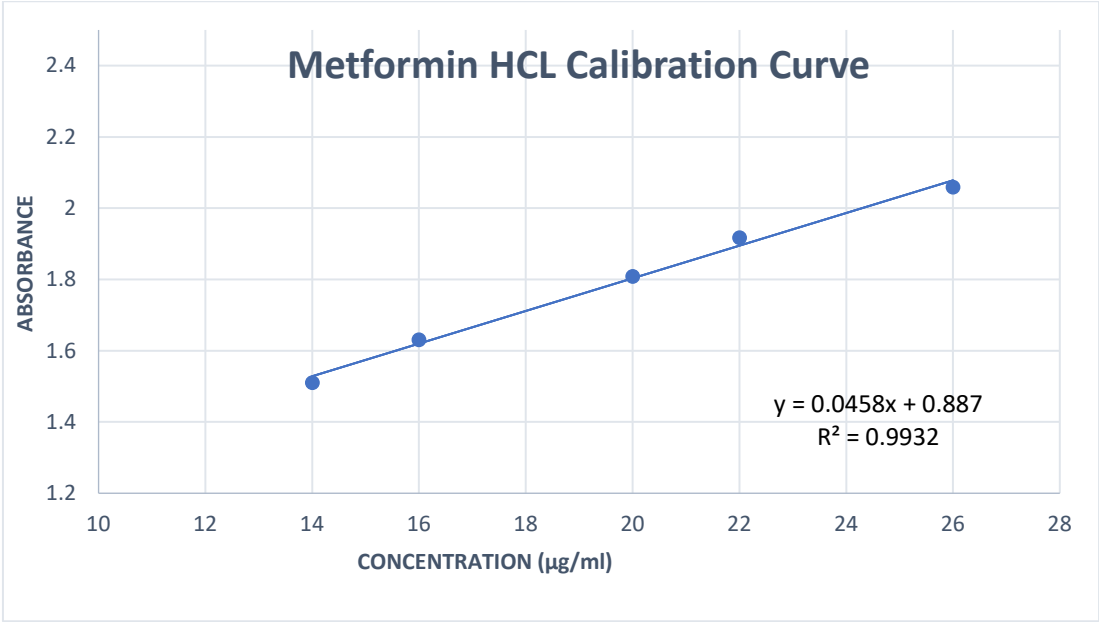


Figure 1 Calibration curve

Post-Formulation studies

Post Compression Studies

Table 5 displays the findings for the formulations F1–F9's hardness, friability, thickness, diameter, and average weight.

Hardness test

Table 5 shows metformin mucoadhesive tablet formulations' hardness levels ranging from 7.995 to 14.085 kg/cm2, below the 10-15 kg/cm^2 range.

Friability test

All formulations (F1 through F9) had a percentage friability ranging from 0.2% to 1.3%. Table 5 displays the tablet friability data.

Thickness test

The tablets' average thickness was 4 to 4.9 mm, and all formulations were within the permitted limits. Table 5 displays a range of tablet thicknesses.

Weight variation test

The weight variation for tablets of different formulations ranged from 597mg to 605mg. Table 5 displays the tablet weight range.

Diameter

Table 5 shows that the diameter of formulations F1 through F9 varied from 11.8 to 12.1 mm.

Table 5 Post Compression Studies

Formulation	Hardness (kg/cm ²)	Friability (%)	Thickness (mm)	Diameter (mm)	Average weight (mg)
F1	8.974	1.9	4.0±5	11.9±2	597±5
F2	9.55	2	4.4±5	11.8±2	602±5
F3	8.447	1.3	4.5±5	12.1±2	600±5
F4	10.486	3.3	4.2±5	11.9±2	605±5
F5	8.915	0.5	4.3±5	12.0±2	599±5
F6	9.66	0.4	4.2±5	12.1±2	601±5
F7	8.365	0.6	4.3±5	12,0±2	604±5
F8	7.995	0.7	4.5±5	11.9±2	598±5
F9	14.085	0.2	4.1±5	12.0±2	599±5

Disintegration Test

In vitro disintegration studies were also conducted on Metformin mucoadhesive tablets. When the appropriate medium was added, the disintegration equipment containing sustained-release mucoadhesive tablets showed no disintegration.

Differential Scanning Calorimetry (DSC)

The DSC findings show that endothermic activity was seen at two distinct temperature ranges, as shown in (Figure 2). The endothermic phenomena revealed two distinct peaks: one between 62°C and 83°C and the other between 215°C and 224°C.

Thermal Gravimetric Analysis

The TGA data showed that the sample remained stable between 0°C and 60°C, but increased temperatures over 80°C caused significant deterioration and weight fluctuations. At temperatures above 230°C, the melting point of metformin, a distinct peak, indicated degradation, which persisted as the temperature increased. Figure 2 displays the graph.

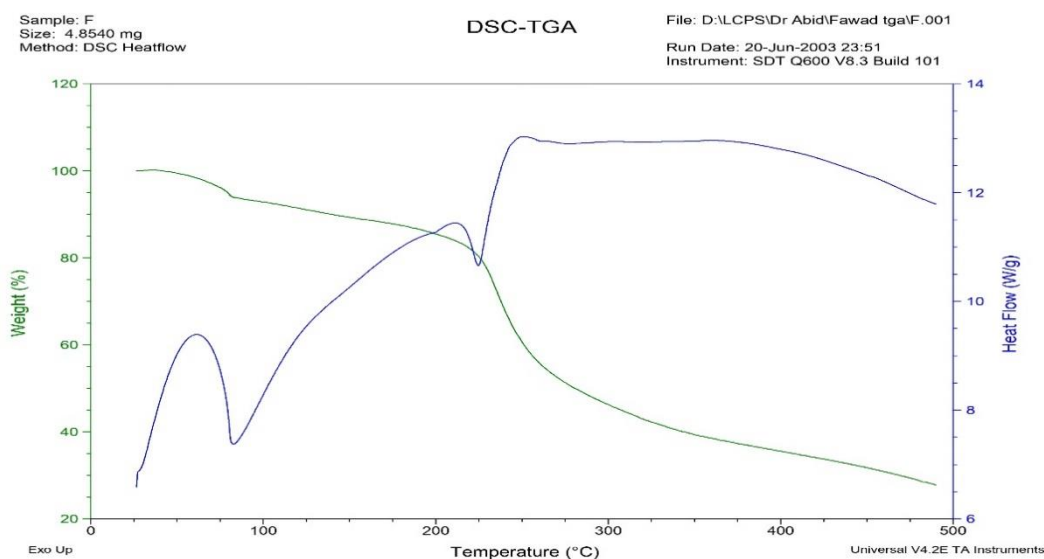


Figure 2 DSC & TGA Curve

X-ray Diffraction

The X-ray diffraction analysis revealed clear and robust peaks in the spectra, indicating a well-defined crystalline structure of the pure metformin powder. In Figure 3, specific peaks were observed at 2θ values of 8, 17.04, and 21.8. A decrease in the drug's crystallinity is suggested, as the metformin peaks were significantly diminished in the presence of the excipient.

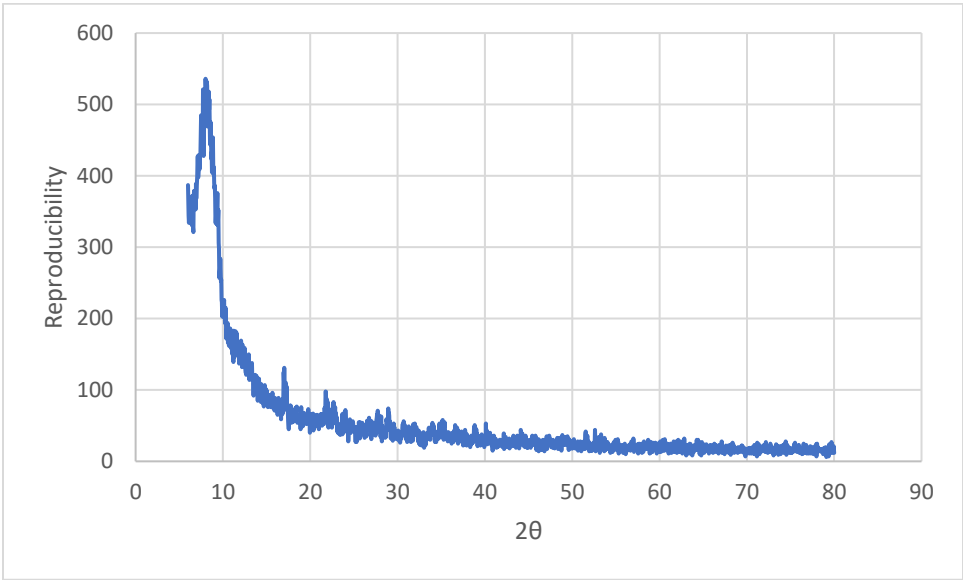


Figure 3 X-ray Diffraction Curve

Invitro analysis

Percentage release

The drug-release characteristics of metformin were examined through in vitro dissolving tests on metformin mucoadhesive tablets. It was noted that the medication dissolution rate increased steadily in all formulations for up to 12 hours, from F1 to F9. 80% release after 10 hours of drug release, which was observed over 12 hours for most of the formulations, except F9 and the initial period exhibited relatively slow release, with most formulations showing a similar pattern. All nine formulations demonstrated more than 50% drug release within 4 hours, except for F4. Additionally, the study found that formulation F7 exhibited the maximum drug release over the 12-hour, at 101.16%. Table 6 displays the proportion of drug release.

Table 6 Data for cumulative in vitro drug release for all formulations (Figure 4)

Time (Hours)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0.5	28.02	27.27	23.16	24.67	21.49	20.33	25.22	19.87	17.19
1	32.73	30.66	28.17	27.94	29.12	34.87	37.52	30.3	29.25
1.5	41.35	34.04	32.56	31.4	32.74	45.29	49.41	40.27	37.48
2	49.97	37.42	36.94	34.87	36.36	54.11	60.11	49.5	47.54
3	58.99	50.96	43.62	44.25	47.61	63.26	71.26	58.46	55.92
4	75.45	57.3	50.3	49.15	51.22	71.18	80.18	66.09	61
6	86.43	64.92	64.49	61.79	62.47	79.74	88.74	73.71	67.56
8	92.8	72.53	75.76	72.81	76.54	85.15	94.15	81.46	72.18
10	94.89	87.33	85.69	80.96	84.17	90.87	97.87	87.26	78.24
12	-	91.67	-	90.65	92.85	95.16	101.16	90.01	83.88

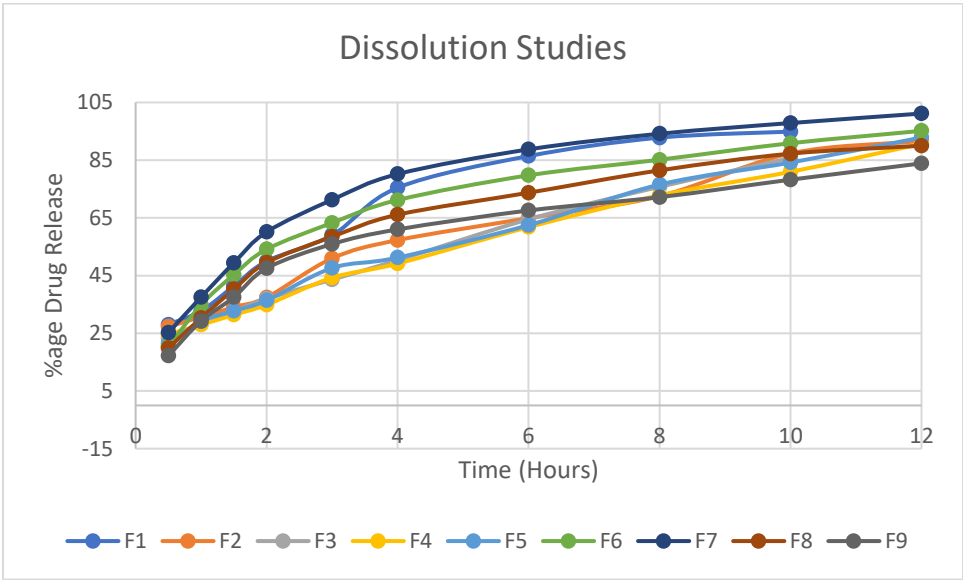


Figure 4 The study examines the in vitro drug release characteristics of metformin from mucoadhesive tablets.

Release kinetic

First-order, zero-order, and Korsmeyer-Peppas release kinetic models were among the models used to assess in vitro dissolution studies. The Korsmeyer-Peppas model was evaluated by using the n-exponent value. Metformin mucoadhesive tablet release studies identified formulations F1 through F9 with an n-value of less than 0.45. Table 7 provides the release kinetics model data. Analysis of regression square values in kinetic models indicated that the formulation for metformin follows first-order release kinetics. The formulation F7 exhibited the highest regression square value of 0.9879.

Table 7 Release kinetic models

Formulations	Zero Order		First Order		Korsmeyer Peppas	
	K0	R(Sequare)	K1	R(Sequare)	kKP	N
F1	12.462	0.2192	0.348	0.9635	37.212	0.435
F2	9.284	0.3549	0.218	0.8724	30.262	0.443
F3	10.084	0.5356	0.199	0.8915	26.691	0.497
F4	8.863	0.5419	0.188	0.8971	26.412	0.486
F5	9.170	0.5620	0.202	0.9240	27.070	0.491
F6	10.374	-0.0767	0.339	0.9496	38.680	0.381
F7	11.307	-0.2595	0.439	0.9879	43.865	0.362
F8	9.790	0.0854	0.279	0.9301	34.978	0.401
F9	8.958	-0.0149	0.227	0.8230	32.917	0.388

4. DISCUSSIONS

The particle size distribution affects physical and chemical properties like solubility, flowability, and surface reaction. The sieve analysis determines particle size distribution for tablet compression. Smaller particles have poor flow due to cohesive forces and gravitational forces. As particle size increases, glidant can be used to enhance the flow. Melting point is a colligative property used to identify compounds and determine their purity. Our drug metformin's official melting point is 221°C, but our observed value is 223°C. The 2% deviation from the US Pharmacopeia's 2% acceptance range indicates the compound is pure and the procedure is not susceptible to human error or apparatus error. These results support the purity of our compound.

The study found that F8 and F9 exhibit excellent flow properties, with angle of repose values ranging from 28.8 ± 1.91 to 56.75 ± 7.96 , with minor deviations due to factors like moisture, shape, and size affecting material angle of repose. Carr's index and Hausner's ratio are used to measure powder compressibility and flow characteristics. Carr's index indicates the powder's compressibility, with formulations ranging from 16.4% to 21.4%. However, Hausner's ratio shows how well the powder compresses; formulas in the range of 1.2 to 1.15 suggest good flow qualities. Both factors are crucial in evaluating powder properties. Indicating its highest solubility, metformin's solubility peak is observed at 7.4 in a neutral pH buffer.

The drug's concentration in aqueous solvent was higher than in organic solvent, indicating its hydrophilic nature. The log P value indicated a higher concentration in the aqueous phase, indicating a higher compound concentration. In phosphate buffer, a hydrophilic drug solubility profile was observed at 7.4 pH. The standard calibration curve is linear, with an R square value of 0.9932, indicating its suitability for measuring unknown drug concentrations. Endothermic activity was noted at two distinct temperature ranges, and the graph in Figure illustrates the DSC data. The first sharp peak of the endothermic phenomenon occurred from 62°C to 83°C ; in comparison, the second sharp peak was observed in the range of 215°C to 224°C (Endothermic reactions are responsible for the heat absorption from the surroundings).

Compound melting is responsible for this change, which hot-stage microscopy verified. The exothermic transition observed directly following the melt is due to the decomposition of the sample. In their study, 'Sustained-release matrix tablets of metformin hydrochloride in combination with tri acetyl-b-cyclodextrin,' observed comparable peaks in DSC (Corti et al., 2008). The sample exhibited stability between 0°C and 60°C , but as temperature rose above 80°C , significant degradation and weight variation were observed despite retaining stability. At metformin's melting point of 230°C , a clear peak signifying deterioration was seen. This degradation continued as the temperature increased further.

Comparable Thermogravimetric analysis (TGA) results were noted by Priyadarshini et al., (2016) during their study on Gastroretentive extended release of metformin from methacrylamide-g-gellan and tamarind seed gum composite matrix. The X-ray diffraction analysis showed clear, robust peaks in the spectra of pure metformin powder, indicating a well-defined crystalline structure. The presence of metformin in the tablet formulation led to a slight decrease in specific peaks at 2θ values 8, 17.04, and 21.8. The presence of metformin in the tablet formulation led to a slight decrease in specific peaks at 2θ values 8, 17.04, and 21.8. The average hardness for formulations F1 through F4 was discovered to be, in turn, 5.7 kg, 7.5 kg, 7.3 kg, and 3.05 kg. The hardness values for formulations F5 to F9 ranged from 7.995 to 14.085 kg/cm².

In their study on the pH-dependent and Ph-independent methacrylate Polymers in the Formulation and Evaluation of Metformin Hydrochloride Sustained Release Sublingual Tablets, Wadher et al., (2011) noted similar patterns for hardness. The friability test performed for formulations F1 to F4 failed due to tablet breakage. These formulations did not meet the official limit required for sustained-release mucoadhesive tablets. However, the friability test for formulations F5 to F9 showed values ranging from 0.2% to 0.7%, indicating that they fell within the official limit. During the design and in vitro and in vivo assessment of mucoadhesive matrix pellets containing metformin hydrochloride for oral controlled release, Ige and Gattani, (2012) noted a similar trend in surface pH a technical depiction.

The thickness of the tablets for these formulations was in the range of 4.6 to 4.5mm. The formulas F5 through F9 have diameters between 11.8- and 12.1-mm. Formulations F5 through F9 have an average weight that falls between 597 ± 0.5 and 605 ± 5 mg. Among those formulations, F7's performance was determined to be the finest and most exceptional in terms of meeting the requirements needed for a sustained-release mucoadhesive formulation. The dissolution analysis gives us the absorbance values at different wavelengths (230-234nm for metformin). We compare these values with the standard calibration curve and find the actual yield. The actual yield is then divided by the theoretical yield, and the whole factor is multiplied by 100 to calculate the percentage of drug release.

The formulation F7, which contained optimal pectin, xanthan gum, and microcrystalline cellulose, exhibited a superior release profile. Our investigation revealed that due to the breakdown of salivary enzymes, 15.5% of the formulation was released after 0.5 hours. After twelve hours, all nine formulations except F1 and F3 showed drug release above 83.88%. F1 and F3 exhibited drug releases of 94.89% and 85.69%, respectively. Formulation F7 demonstrated the maximum drug release, approximately 101.16%, at twelve hours. The release profiles of all formulations indicated sustained drug release. Over a specific amount of time, a comparable pattern of drug release was noted by Mandal et al., (2007) in their study, Metformin HCl 500 mg sustained-release matrix tablet formulation and optimization utilizing response surface methods.

The n-exponent of the Korsmeyer and Peppas models suggested Fickian drug release. The Korsmeyer-Peppas model, zero-order and first-order kinetics, and a goodness-of-fit test using linear regression analysis were applied to the in vitro drug release data of all mucoadhesive tablet formulations of metformin HCl to determine the drug release mechanism. The release studies of metformin mucoadhesive tablets showed that formulations F1 to F9 had n values of about 0.45 or less, indicating that all formulations followed Fickian drug release transport, resulting in a sustained release effect. Similarly, over a specified period, Fickian drug release was observed by Mandal et al., (2007) in their study, Metformin HCl 500 mg sustained-release matrix tablet formulation and optimization utilizing response surface methods.

5. CONCLUSION

Natural and biocompatible mucoadhesive polymers were employed to produce mucoadhesive metformin tablets, an antidiabetic drug used to treat type 2 diabetes mellitus. After a successful synthesis of the mucoadhesive formulation, all pre- and post-compression characterizations were determined to be within the ideal range. Thermal stability was evaluated by DSC, indicating that the drug remained thermally stable. The crystallinity of the drug was assessed through XRD, revealing a decrease in metformin crystallinity due to the presence of excipients.

The study found that increasing mucoadhesive polymer in a tablet decreases its release rate. Release kinetics modeling, conducted through regression analysis, revealed sustained release patterns. Among all formulations, the results of F7 were excellent and met the standards required for sustained-release mucoadhesive formulation. Since the formulation meets official standards, it can offer optimal drug delivery and therapeutic outcomes.

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Author Contributions

	Muhammad Abid Mustafa	Asad Majeed Khan	Muhammad Hassan	Hanza Saeed	Fatima Sabir	Iqra Mushfaq	Namra Rasheed	Iqra Rasheed	Muhammad Arsh	Minahil Arif	Afshan Abdul Shakoore
Conceived & designed	✓	✓	✓	✓	✗	✓	✗	✗	✗	✗	✗
Collected & analyzed data	✓	✗	✓	✓	✓	✓	✓	✓	✓	✓	✗
Wrote manuscript	✓	✓	✓	✓	✗	✗	✗	✓	✗	✗	✓
Read & approved manuscript.	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Informed Consent

Not applicable

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Conflict of interest

The authors declare that there is no conflict of interests.

Data and materials availability

All data sets collected during this study are available upon reasonable request from the corresponding author.

REFERENCES

- Ahmed F, Mustafa MA, Tayyab M, Sarwer MU, Khan HU, Zahee L. Fabrication and In vitro Evaluation of Chitosan-based Nanocomposites through Ionic Gelation Method for the Sustained Release Drug Delivery of Nicorandil. *AJPRHC* 2023; 15(4):338-346. doi: 10.4103/ajprhc.ajprhc_110_23
- Bahulkar SS, Munot NM, Surwase SS. Synthesis, characterization of thiolated karaya gum and evaluation of effect of pH on its mucoadhesive and sustained release properties. *Carbohydr Polym* 2015; 130:183-190. doi: 10.1016/j.carbpol.2015.04.064
- Boddupalli BM, Mohammed ZN, Nath RA, Banji D. Mucoadhesive drug delivery system: An overview. *J Adv Pharm Technol Res* 2010; 1(4):381-387. doi: 10.4103/0110-5558.76436
- Corti G, Cirri M, Maestrelli F, Mennini N, Mura P. Sustained-release matrix tablets of metformin hydrochloride in combination with triacetyl- β -cyclodextrin. *Eur J Pharm Biopharm* 2008; 68(2):303-309. doi: 10.1016/j.ejpb.2007.06.004
- Dhar S, Pokharkar V. Formulation Development of mucoadhesive matrix tablet for metformin hydrochloride: in-vitro and in-vivo evaluation. *Res J Pharm Technol* 2010; 3(2):483-489.
- Giannarelli R, Aragona M, Coppelli A, Del-Prato S. Reducing insulin resistance with metformin: the evidence today. *Diabetes Metab* 2003; 29(4 Pt 2):6S28-35. doi: 10.1016/s1262-3636(03)72785-2
- Ige PP, Gattani SG. Design and in vitro and in vivo characterization of mucoadhesive matrix pellets of metformin hydrochloride for oral controlled release: a technical note. *Arch Pharm Res* 2012; 35(3):487-98. doi: 10.1007/s12272-012-0312-7
- Jannot Y, Felix V, Degiovanni A. A centered hot plate method for measurement of thermal properties of thin insulating materials. *Meas Sci Technol* 2010; 21:035106. doi: 10.1088/0957-0233/21/3/035106
- Mandal U, Gowda V, Ghosh A, Selvan S, Solomon S, Pal TK. Formulation and optimization of sustained release matrix tablet of metformin HCl 500 mg using response surface methodology. *Yakugaku zasshi* 2007; 127:1281-1290. doi: 10.1248/yakushi.127.1281
- Menczel JD, Judovits L, Prime RB, Bair HE, Reading M, Swier S. Differential scanning calorimetry (DSC). *Thermal analysis of polymers: Fundamentals and applications* 2008; 7-239. doi: 10.1002/9780470423837
- Mustafa MA, Khan AM, Ali N, Ahmed F, Latif MU, Shahid Z, Akram M, Ijaz A, Arif M, Ilyas A. Formulation and in vitro Evaluation of pH Dependent Colon Targeted Controlled Release Tablet of Mesalamine Containing Cyamopsis tetragonoloba Gum and Sodium Alginate. *Int J Pharm Investig* 2023a; 13(3):476-484. doi: 10.5530/ijpi.13.3.059
- Mustafa MA, Ur-Rehman NS, Khan AM, Munir M, Azhar K, Ahmed F, Imran A, Arif M, Latif MU, Ijaz A. Formulation and in vitro Evaluation of Natural Polymer Based Albendazole Gummies: A Novel Pediatrics Dosage Form. *J Young Pharm* 2023b; 15(3):478-484. doi: 10.5530/jyp.2023.15.63
- Priyadarshini R, Nandi G, Changder A, Chowdhury S, Chakraborty S, Ghosh LK. Gastroretentive extended release of metformin from methacrylamide-g-gellan and tamarind seed gum composite matrix. *Carbohydr. Polym* 2016; 137:100-110. doi: 10.1016/j.carbpol.2015.10.054
- Sarkar D, Nandi G, Changder A, Hudati P, Sarkar S, Ghosh LK. Sustained release gastroretentive tablet of metformin hydrochloride based on poly (acrylic acid)-grafted-gellan. *Int J Biol Macromol* 2017; 96:137-148. doi: 10.1016/j.ijbiomac.2016.12.022
- Shurrab NT, Arafa ESA. Metformin: A review of its therapeutic efficacy and adverse effects. *Obes Med* 2020; 17:100186. doi: 10.1016/j.obmed.2020.100186
- United States Pharmacopeia. USP 41 - NF 36 The United States Pharmacopeia and National Formulary 2018: Main Edition Plus Supplements 1 and 2, 2017.
- Unnikrishnan R, Pradeepa R, Joshi SR, Mohan V. Type 2 diabetes: demystifying the global epidemic. *Diabetes* 2017; 66(6):1432-1442. doi: 10.2337/db16-0766
- Wadher KJ, Kakde RB, Umekar MJ. Formulation and evaluation of sustained release matrix tablets of metformin hydrochloride using pH dependent and pH independent

- methacrylate polymers. J Pharm Res Int 2011; 1(2):29-45. doi: 10.9734/BJPR/2011/255
19. Wójcik-Pastuszka D, Krzak J, Macikowski B, Berkowski R, Osiński B, Musiał W. Evaluation of the release kinetics of a pharmacologically active substance from model intra-articular implants replacing the cruciate ligaments of the knee. Mater (Basel) 2019; 12(8):1202. doi: 10.3390/ma12081202
20. Wu B, Deng D, Lu Y, Wu W. Biphasic release of indomethacin from HPMC/pectin/calcium matrix tablet: II. Influencing variables, stability and pharmacokinetics in dogs. Eur J Pharm Biopharm 2008; 69(1):294-302. doi: 10.1016/j.ejpb.2007.10.001